Drug Class Review
on
Calcium Channel Blockers

Update #3: Preliminary Scan Report

December 2006

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:
Original Final Report March 2005 (searches through February 2004)

SCOPE AND KEY QUESTIONS:

The purpose of this review is to compare the benefits and harms of calcium channel blockers when used to treat hypertension, supraventricular arrhythmias, angina or .left ventricular dysfunction. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. Do CCBs differ in effectiveness in the treatment of adult patients with essential hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (left ventricular ejection fraction [LVEF] <45%)?
2. Do CCBs differ in their safety or adverse effects in the treatment of adult patients with essential hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (LVEF<45%)?
3. Based on demographics (age, racial groups, gender), other medications, or comorbidities, are there subgroups of patients for which one CCB is more effective or is associated with fewer adverse effects?

Inclusion Criteria

Population
Adults with hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmia or supraventricular tachycardia (SVT), and systolic dysfunction (LVEF <45%).

Interventions
Amlodipine

Bepridil
Diltiazem
Felodipine
Isradipine
Nicardipine
Nifedipine
Nisoldipine
Verapamil

Outcomes

Hypertension
All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Development of renal failure (end stage renal disease/dialysis/transplant/ Clinically significant, permanent increase in serum creatinine or decrease in creatinine clearance)
Quality of Life

Angina
All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Symptoms
Quality of Life

Supraventricular Arrhythmias
All cause mortality
Cardiovascular (CV) disease mortality
Stroke
Symptoms (rate or rhythm control)
Quality of Life

Left-ventricular Dysfunction
All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Symptoms
Quality of Life

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE (February 2004 to December 2006). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs,

indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

We identified 165 potentially relevant citations. Of those, there are 24 potentially relevant controlled clinical trials (Appendix A). Some of these are further analyses of trials previously include (e.g. ALLHAT).

New Drugs

None identified.
Bepridil discontinued due to ventricular arrhythmias.
CCBs found in new trials but not currently on US market: ‘cilnidipine’, 'benidipine', 'nilvadipine'

New Indications

Amlodipine indicated for use in patients with angiographically documented coronary artery disease– expanded population (9/05).

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New Safety Alerts

Several products required to strengthen language on potential pro-arrhythmic effects

APPENDIX A

Unknown Study design (no abstract)

1. Logan A. BENEDICT in the treatment of hypertension. *Current Hypertension Reports.* Apr 2005;7(2):121-123.

Active-Controlled Trials

2. Black HR, Elliott WJ, Grandits G, et al. Results of the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial by geographical region. *Journal of Hypertension.* May 2005;23(5):1099-1106.

OBJECTIVE: To examine regional differences in the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial. DESIGN: Double-blind, randomized, international clinical trial. SETTING: Six hundred and sixty-one clinical centers in 15 countries. PATIENTS: Hypertensive volunteers (n = 16,602) with > or =1 additional cardiovascular risk factor, grouped into four regions: USA (n = 8144), Canada (n = 3405), Western Europe (Spain, UK, Italy, Sweden, Germany; n = 2048) or 'other' (Bulgaria, Israel, Mexico, Czech Republic, Hungary, Poland, Slovakia, Brazil; n = 2879); subgroupings included country and state/province within the USA and Canada. INTERVENTIONS: Randomized to COER-verapamil or the investigator's choice of either atenolol or hydrochlorothiazide, titrated and additional drugs added as required. MAIN OUTCOME MEASURES: Baseline characteristics; blood pressure control, medication adherence and lost-to-follow-up at 2 years; and composite primary endpoint (stroke, myocardial infarction, cardiovascular death) by regional groupings. RESULTS: Regional differences were found at baseline for age, gender, blood pressure, percentage receiving antihypertensive drug therapy, initial choice of atenolol or hydrochlorothiazide, and risk factor profile. Blood pressure control rates increased markedly during follow-up in all regions, but varied significantly by region. Blood pressure control, medication adherence and lost-to-follow-up rates were poorest in the USA. After adjustment for baseline differences, the primary-event rate for each region was significantly lower than for the USA. Although baseline factors, blood pressure control and event rates varied by region, treatment differences did not. CONCLUSION: Despite differences in baseline and follow-up measures across geographical regions, the absence of treatment differences by region suggests that the overall findings of CONVINCE are robust.

3. Cooper-Dehoff R, Cohen JD, Bakris GL, et al. Predictors of development of diabetes mellitus in patients with coronary artery disease taking antihypertensive medications (findings from the INternational VErapamil SR-Trandolapril STudy [INVEST]). *American Journal of Cardiology.* Oct 1 2006;98(7):890-894.

Knowledge of predictors of diabetes mellitus (DM) development in patients with coronary artery disease (CAD) who use antihypertensive therapy could contribute to decreasing this adverse metabolic consequence. This is particularly relevant because the standard of care, beta blockers combined with diuretics, may contribute to adverse metabolic risk. The INternational VErapamil SR-trandolapril STudy compared a calcium antagonist-based (verapamil SR) and a beta-blocker-based (atenolol) strategy with trandolapril and/or hydrochlorothiazide added to control blood pressure (BP) in patients with CAD. The 16,176 patients without DM at entry were investigated with regard to newly diagnosed

DM during follow-up. Newly diagnosed DM was less frequent in the verapamil SR versus atenolol strategy (7.0% vs 8.2%, hazard ratio 0.85, 95% confidence interval 0.76 to 0.95, p <0.01). Characteristics associated with risk for newly diagnosed DM included United States residence, left ventricular hypertrophy, previous stroke/transient ischemic attack, Hispanic ethnicity, coronary revascularization, hypercholesterolemia, greater body mass index, and higher follow-up systolic BP. Addition of trandolapril to verapamil SR decreased DM risk and addition of hydrochlorothiazide to atenolol increased risk. In conclusion, clinical findings associated with more severe vascular disease and Hispanic ethnicity identify a group at high risk for developing DM, whereas lower on-treatment BP and treatment with verapamil SR-trandolapril attenuated this risk.

4. de Leeuw PW, Ruilope LM, Palmer CR, et al. Clinical significance of renal function in hypertensive patients at high risk: results from the INSIGHT trial.[see comment]. *Archives of Internal Medicine.* Dec 13-27 2004;164(22):2459-2464.

BACKGROUND: Increasing evidence suggests renal involvement in hypertension-related cardiovascular and cerebrovascular complications. To assess this role of renal function in more detail, we studied the evolution of renal function and the relationship of renal function with mortality and morbidity in the Intervention as a Goal in Hypertension Treatment (INSIGHT) study. METHODS: The INSIGHT study was a double-blind, randomized, multicenter trial in patients with hypertension and at least 1 additional cardiovascular risk factor. Treatment consisted of nifedipine gastrointestinal therapeutic system, 30 mg/d, or hydrochlorothiazide-amiloride (25 mg/d of hydrochlorothiazide and 2.5 mg/d of amiloride hydrochloride). Primary outcome was a composite of cardiovascular death, myocardial infarction, heart failure, and stroke. Renal function was assessed by measuring creatinine clearance, serum creatinine level, and serum uric acid level and by the presence of proteinuria. RESULTS: Creatinine clearance fell more in nifedipine recipients than in hydrochlorothiazide-amiloride recipients. Renal insufficiency developed in 2% of nifedipine recipients and 5% of hydrochlorothiazide-amiloride recipients. Primary outcomes occurred in 15% of patients with increased serum creatinine levels and 6% of patients with normal levels (odds ratio [OR] 2.89; 95% confidence interval [CI], 1.92-4.36; P<.001). Primary outcomes were more likely in patients with low creatinine clearance (<60 mL/min) than in those with higher clearances (9% vs 5%, respectively [OR, 1.51, 95%CI, 1.22-1.88; P<.001]). CONCLUSIONS: Renal function is an important predictor of risk in hypertensive patients at high risk. Antihypertensive treatment with a long-acting dihydropyridine calcium channel blocker may better preserve renal function than would treatment with diuretics.

5. Derosa G, Cicero AFG, Bertone G, et al. Comparison of the effects of telmisartan and nifedipine gastrointestinal therapeutic system on blood pressure control, glucose metabolism, and the lipid profile in patients with type 2 diabetes mellitus and mild hypertension: a 12-month, randomized, double-blind study. *Clinical Therapeutics.* Aug 2004;26(8):1228-1236.

BACKGROUND: Angiotensin receptor blockers (ARBs) provide effective blood pressure control. Whereas none of the ARBs appear to affect glucose homeostasis, some ARBs have been associated with a decrease in cholesterolemia. OBJECTIVE: This study was conducted to evaluate blood pressure control glucose homeostasis, and the plasma lipid profile in patients with type 2 diabetes mellitus and mild hypertension during 12 months

of treatment with the ARB telmisartan or nifedipine gastrointestinal therapeutic system (GITS). METHODS: In this double-blind trial, patients taking oral hypoglycemic agents were randomized to receive telmisartan 40 mg or nifedipine GITS 20 mg once daily for 12 months. At the time of enrollment, patients were given advice on diet (1400-1600 kcal/d) and exercise (stationary bicycle for > or =30 min, 4 d/wk). Assessments of systolic blood pressure (SBP), diastolic blood pressure, body mass index (BMI), fasting plasma glucose concentrations, glycosylated hemoglobin, fasting plasma insulin concentrations, the homeostasis model assessment of insulin resistance, and the lipid profile were performed at baseline and after 6 and 12 months of treatment. RESULTS: One hundred sixteen patients were divided into 2 age- and sex-matched treatment groups (58 men, 58 women; mean [SD] age, 52.5 [5] years). All patients were in good general health at baseline; had achieved adequate glycemic control with diet and oral hypoglycemic agents; were taking antihypercholesterolemic drugs; and had no evidence of macroangiopathy, microalbuminuria, or neuropathy. There were significant reductions from baseline in seated trough SBP after 12 months of treatment with both telmisartan and nifedipine GITS (from 139 [4] to 132 [4] mm Hg and from 140 [4] to 130 [4] mm Hg, respectively; both, P < 0.01). No change in BMI or glucose metabolism was observed with either treatment. After 12 months, there were significant improvements in concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) with telmisartan (-9% and -11.5%, respectively; both, P < 0.01) compared with nifedipine GITS (-2% and -1.5%). CONCLUSIONS: In this selected sample of patients with type 2 diabetes and mild hypertension, both telmisartan and nifedipine GITS produced significant reductions in blood pressure. Telmisartan was associated with a slight but statistically significant improvement in plasma TC and LDL-C concentrations compared with nifedipine GITS.

6. Frishman WH, Hainer JW, Sugg J, Group MFS. A factorial study of combination hypertension treatment with metoprolol succinate extended release and felodipine extended release results of the Metoprolol Succinate-Felodipine Antihypertension Combination Trial (M-FACT). *American Journal of Hypertension.* Apr 2006;19(4):388-395.

BACKGROUND: Many hypertensive patients require combination therapy to achieve target blood pressure (BP). beta-Blockers and dihydropyridine calcium channel blockers are effective as monotherapy in hypertensive patients and have complementary mechanisms for lowering BP. METHODS: This multicenter, randomized, placebo-controlled, unbalanced factorial study included a 4- to 5-week single-blind placebo, 9-week, double-blind treatment as well as a 2-week double-blind, down-titration period. Patients (N = 1092) were randomized to one of 16 treatment groups: extended-release (ER) metoprolol succinate (25, 100, or 400 mg), ER felodipine (2.5, 10, or 20 mg), ER felodipine/ER metoprolol succinate (2.5/25, 2.5/100, 2.5/400, 10/25, 10/100, 10/400, 20/25, 20/100, or 20/400 mg), or placebo. RESULTS: At baseline, treatment groups were well balanced; mean sitting BP was 152.6/99.9 mm Hg. Monotherapy with ER metoprolol succinate induced dose-related reductions in sitting systolic/diastolic BP (DBP) (mean 8.1/7.7 to 9.7/11.1 mm Hg) as did ER felodipine (mean 7.7/7.7 to 14.0/11.8) and the combinations reflected additive effects (mean 13.8/11.0 to 19.8/15.2). The decline in the placebo group was 2.1/4.0 mm Hg. All combinations were more effective than their components (P < .05 for all but ER metoprolol succinate 25/ER felodipine 20). When compared with the

highest doses of the individual agents (ER metoprolol succinate 400 mg; ER felodipine 20 mg), the low-dose combination ER metoprolol succinate 25/ER felodipine 2.5 was approximately as effective (differences in DBP <1 mm Hg). The most common adverse events leading to discontinuation were peripheral edema (4%), headache (2%), and fatigue (1%). Higher rates of peripheral edema and flushing were associated with high-dose ER felodipine, either alone or in combination. CONCLUSIONS: The antihypertensive effects of ER metoprolol succinate and ER felodipine are dose-related, and when given in combination, their BP-lowering effects are additive over a wide dose range. Low-dose combination therapy is comparable in effectiveness to high-dose monotherapy but is better tolerated.

7. Hemels MEW, Van Noord T, Crijns HJGM, et al. Verapamil versus digoxin and acute versus routine serial cardioversion for the improvement of rhythm control for persistent atrial fibrillation. *Journal of the American College of Cardiology.* Sep 5 2006;48(5):1001-1009.

OBJECTIVES: The VERDICT (Verapamil Versus Digoxin and Acute Versus Routine Serial Cardioversion Trial) is a prospective, randomized study to investigate whether: 1) acutely repeated serial electrical cardioversions (ECVs) after a relapse of atrial fibrillation (AF); and 2) prevention of intracellular calcium overload by verapamil, decrease intractability of AF. BACKGROUND: Rhythm control is desirable in patients suffering from symptomatic AF. METHODS: A total of 144 patients with persistent AF were included. Seventy-four (51%) patients were randomized to the acute (within 24 h) and 70 (49%) patients to the routine serial ECVs, and 74 (51%) patients to verapamil and 70 (49%) patients to digoxin for rate control before ECV and continued during follow-up (2 x 2 factorial design). Class III antiarrhythmic drugs were used after a relapse of AF. Follow-up was 18 months. RESULTS: At baseline, there were no significant differences between the groups, except for beta-blocker use in the verapamil versus digoxin group (38% vs. 60%, respectively, p = 0.01). At follow-up, no difference in the occurrence of permanent AF between the acute and the routine cardioversion groups was observed (32% [95% confidence intervals (CI)] 22 to 44) vs. 31% [95% CI 21 to 44], respectively, p = NS), and also no difference between the verapamil- and the digoxin-randomized patients (28% [95% CI 19 to 40] vs. 36% [95% CI 25 to 48] respectively, p = NS). Multivariate Cox regression analysis revealed that lone digoxin use was the only significant predictor of failure of rhythm control treatment (hazard ratio 2.2 [95% CI 1.1 to 4.4], p = 0.02). CONCLUSIONS: An acute serial cardioversion strategy does not improve long-term rhythm control in comparison with a routine serial cardioversion strategy. Furthermore, verapamil has no beneficial effect in a serial cardioversion strategy.

8. Inoue S, Tomino Y. Effects of calcium antagonists in hypertensive patients with renal dysfunction: a prospective, randomized, parallel trial comparing benidipine and nifedipine. *Nephrology.* Oct 2004;9(5):265-271.

BACKGROUND: Although calcium antagonists, derived from dihydropyridine (DHP), are important agents in achieving control in a majority of patients with high blood pressure and renal disease, there are no comparative data regarding their inhibitory effects on the progression of renal dysfunction in Japan. METHODS: Benidipine and nifedipine retard both calcium antagonists derived from DHP and were compared in terms of their inhibitory effect on the progression of renal dysfunction in hypertensive patients. The

primary end-points were defined as 1.5 times the serum creatinine value at baseline, progression to end-stage renal failure (ESRF) necessitating dialysis or renal transplantation, and death. RESULTS: During the study period, a significant decline in blood pressure was observed in the two groups, with no significant difference between them. The worsening of nephropathy was significantly inhibited in the benidipine group as compared with the nifedipine retard group (log-rank test: P = 0.014, Wilcoxon's test: P = 0.022). Among the subjects who reached a primary end-point, one (33%) in the benidipine group and five (50%) in the nifedipine retard group were placed on haemodialysis within 1 year. CONCLUSION: It appears that benidipine inhibits the progression of hypertensive renal diseases more effectively than nifedipine retard.

9. Investigators JE, Investigators JE. Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Patients With Mild-to-Moderate Hypertension (J-ELAN): rationale and design. *Circulation Journal.* Jan 2006;70(1):124-128.

BACKGROUND: Hypertension is a major underlying disease that may cause left ventricular (LV) diastolic dysfunction, even without LV systolic dysfunction, and antihypertensive drugs could affect LV diastolic function. METHODS AND RESULTS: The Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Patients With Mild-to-Moderate Hypertension (J-ELAN) study is a multicenter, prospective, randomized trial designed to assess the effects of losartan and amlodipine on LV diastolic function in hypertensive patients with LV diastolic dysfunction in the absence of systolic dysfunction. A total of 300 patients (150 patients in each group) will be enrolled. In addition to Doppler echocardiographic indices of LV diastolic function, changes in LV structure and atherosclerosis of the carotid arteries will be serially assessed. The maximum follow-up period is 18 months. CONCLUSIONS: This study will provide the characteristic differences in the effects of amlodipine and losartan on LV diastolic dysfunction in hypertensive patients.

10. Jerums G, Allen TJ, Campbell DJ, et al. Long-term renoprotection by perindopril or nifedipine in non-hypertensive patients with Type 2 diabetes and microalbuminuria. *Diabetic Medicine.* Nov 2004;21(11):1192-1199.

AIMS: To assess the efficacy of an angiotensin converting enzyme (ACE) inhibitor (perindopril), a dihydropyridine calcium channel blocker (sustained release nifedipine) and placebo in preventing the progression of albuminuria and decline in glomerular filtration rate (GFR) in patients with Type 2 diabetes and microalbuminaria. METHODS: A prospective, randomized, open, blinded end point study of 77 patients allocated to three treatment groups (23 perindopril, 27 nifedipine, 27 placebo). Drug doses were adjusted to achieve a decrease in diastolic blood pressure (DBP) of 5 mmHg in the first 3 months and additional therapy was given if hypertension developed (supine DBP > 90 mmHg and/or systolic blood pressure (SBP) > 140 mmHg if < or = 40 years; supine DBP > 90 mmHg and/or SBP > 160 mmHg if > 40 years). Median follow-up was 66 months, with 37 patients being followed for at least 6 years. RESULTS: Blood pressure remained within the non-hypertensive range in 83% of perindopril-, 95% of nifedipine- and 30% of placebo-treated patients (P < 0.01). In the first 12 months albumin excretion rate (AER) decreased by 47% only in the perindopril group (P = 0.04). From 12 to 72 months, AER gradients increased by 27% per year only in the placebo group (P < 0.01). After 6 years, macroalbuminuria had developed in 7/15 placebo compared with 2/11 in perindopril and

1/11 nifedipine-treated patients (P = 0.05). GFR did not change in the first 12 months, but thereafter the median GFR gradient (ml/min/1.73 m(2) per year) was -2.4 (P < 0.01) for perindopril-, -1.3 (P = 0.26) for nifedipine- and -4.2 (P = 0.01) for placebo-treated patients. The rate of decline in GFR for the study group as a whole from 12 months to the end of follow-up correlated negatively with mean arterial pressure (MAP) (r = -0.38, P < 0.01). During a 3-month treatment pause in 29 patients AER tended to increase only in the perindopril group (P < 0.07). CONCLUSIONS: Long-term control of blood pressure with perindopril or nifedipine stabilizes AER and attenuates GFR decline in proportion to MAP in non-hypertensive patients with Type 2 diabetes and microalbuminuria.

11. Koylan N, Bilge AK, Adalet K, Mercanoglu F, Buyukozturk K, Group TTS. Comparison of the effects of trimetazidine and diltiazem on exercise performance in patients with coronary heart disease. The Turkish trimetazidine study (TTS). *Acta Cardiologica.* Dec 2004;59(6):644-650.

OBJECTIVE: A multicentre, double-blind comparative study was performed to compare the effects of trimetazidine with diltiazem on exercise performance in patients with stable angina pectoris. METHODS AND RESULTS: A total of 116 male patients with documented coronary artery disease at 11 centres were randomized into trimetazidine and diltiazem groups both including 58 men (mean age 55.1+/-8.6 years and 54.9+/-6.6 years, respectively) in a prospective, multicentre, double-blind active treatment trial.The study consisted of a two-week placebo washout period and a four-week active treatment phase. Clinical examinations and exercise tests were performed at the beginning (D0) and at the end (D28) of the active treatment. Laboratory investigations were also performed at the beginning of the washout period (D-14) and at D28. Holter recordings were done in the mid of the washout period (D-7) and D28. Both trimetazidine and diltiazem decreased the number of anginal attacks per week (p < 0.0001 for both drugs) and weekly nitrate consumption (p = 0.0008 and p < 0.0001, respectively). Both trimetazidine and diltiazem improved the recovery of anginal pain (p = 0.0188 and p = 0.0079, respectively) and maximal ST-segment depression (p = 0.0134 and p = 0.0214, respectively) but none of the drugs significantly changed the time to 1 mm ST-segment depression and ST recovery time on exercise test. Diltiazem caused a slight prolongation of PR and QRS durations (p = 0.039) on ambulatory ECG whereas trimetazidine did not change these parameters significantly. CONCLUSION: This study suggests that trimetazidine is an effective and safe alternative for diltiazem in the treatment of patients with stable angina pectoris. Although several other trials have shown that this drug can be used in combination with other antianginal drugs or instead of beta blockers or nifedipine in the symptomatic treatment of stable anginal syndromes, this study suggests that trimetazidine can be used instead of diltiazem, a well-known powerful antianginal drug.

12. Leenen FHH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial.[see comment]. *Hypertension.* Sep 2006;48(3):374-384.

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) provides a unique opportunity to compare the long-term relative safety and efficacy of angiotensin-converting enzyme inhibitor and calcium channel blocker-initiated therapy in older hypertensive individuals. Patients were randomized to amlodipine (n=9048) or

lisinopril (n=9054). The primary outcome was combined fatal coronary heart disease or nonfatal myocardial infarction, analyzed by intention-to-treat. Secondary outcomes included all-cause mortality, stroke, combined cardiovascular disease (CVD), end-stage renal disease (ESRD), cancer, and gastrointestinal bleeding. Mean follow-up was 4.9 years. Blood pressure control was similar in nonblacks, but not in blacks. No significant differences were found between treatment groups for the primary outcome, all-cause mortality, ESRD, or cancer. Stroke rates were higher on lisinopril in blacks (RR=1.51, 95% CI 1.22 to 1.86) but not in nonblacks (RR=1.07, 95% CI 0.89 to 1.28), and in women (RR=1.45, 95% CI 1.17 to 1.79), but not in men (RR=1.10, 95% CI 0.92 to 1.31). Rates of combined CVD were higher (RR=1.06, 95% CI 1.00 to 1.12) because of higher rates for strokes, peripheral arterial disease, and angina, which were partly offset by lower rates for heart failure (RR=0.87, 95% CI 0.78 to 0.96) on lisinopril compared with amlodipine. Gastrointestinal bleeds and angioedema were higher on lisinopril. Patients with and without baseline coronary heart disease showed similar outcome patterns. We conclude that in hypertensive patients, the risks for coronary events are similar, but for stroke, combined CVD, gastrointestinal bleeding, and angioedema are higher and for heart failure are lower for lisinopril-based compared with amlodipine-based therapy. Some, but not all, of these differences may be explained by less effective blood pressure control in the lisinopril arm.

13. Mancia G, Ruilope L, Palmer C, et al. Effects of nifedipine GITS and diuretics in isolated systolic hypertension--a subanalysis of the INSIGHT study. *Blood Pressure.* 2004;13(5):310-315.

AIMS: This study tested the effects on cardiovascular outcomes of treatments based on nifedipine gastrointestinal therapeutic system (GITS) compared with the diuretic combination co-amilozide in a pre-specified subset of patients with isolated systolic hypertension (ISH) enrolled in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study. MAJOR FINDINGS: Of 6321 randomized patients, 1498 (23.7%) had ISH with a baseline mean BP of 173/88 mmHg in both treatment groups. Mean BP fell by 29/10 mmHg in the nifedipine and 30/10 mmHg in the diuretic group to a mean BP of 144/78 mmHg and 143/79 mmHg, respectively, at endpoint. The percentage of primary outcomes in patients with ISH was not significantly different between the two treatment groups (nifedipine GITS 6.0%, co-amilozide 6.6%). The number of ISH patients with composite secondary outcomes was 90 (12.2%) in the nifedipine GITS group and 110 (14.5%) in the co-amilozide group (not significant). The incidence rates of primary and secondary outcomes were similar in patients without ISH. CONCLUSION: In patients with ISH, nifedipine GITS and co-amilozide had similar effects on clinical outcomes and BP lowering. They lend support to international guidelines for the treatment of hypertension recommending the use of long-acting dihydropyridine calcium-channel blockers as one treatment option for patients with ISH.

14. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Annals of Internal Medicine.* Jun 20 2006;144(12):884-893.

BACKGROUND: Because coronary perfusion occurs mainly during diastole, patients with coronary artery disease (CAD) could be at increased risk for coronary events if diastolic pressure falls below critical levels. OBJECTIVE: To determine whether low blood

pressure could be associated with excess mortality and morbidity in this population. DESIGN: A secondary analysis of data from the International Verapamil-Trandolapril Study (INVEST), which was conducted from September 1997 to February 2003. SETTING: 862 sites in 14 countries. PATIENTS: 22 576 patients with hypertension and CAD. Interventions: Patients from INVEST were randomly assigned to a verapamil sustained-release- or atenolol-based strategy; blood pressure control and outcomes were equivalent. MEASUREMENTS: An unadjusted quadratic proportional hazards model was used to evaluate the relationship between average on-treatment blood pressure and risk for the primary outcome (all-cause death, nonfatal stroke, and nonfatal myocardial infarction [MI]), all-cause death, total MI, and total stroke. A second model adjusted for differences in baseline covariates. RESULTS: The relationship between blood pressure and the primary outcome, all-cause death, and total MI was J-shaped, particularly for diastolic pressure, with a nadir at 119/84 mm Hg. After adjustment, the J-shaped relationship persisted between diastolic pressure and primary outcome. The MI-stroke ratio remained constant over a wide blood pressure range, but at a lower diastolic blood pressure, there were substantially more MIs than strokes. An interaction between decreased diastolic pressure and history of revascularization was observed; low diastolic pressure was associated with a relatively lower risk for the primary outcome in patients with revascularization than in those without revascularization. LIMITATIONS: This is a post hoc analysis of hypertensive patients with CAD. CONCLUSIONS: The risk for the primary outcome, all-cause death, and MI, but not stroke, progressively increased with low diastolic blood pressure. Excessive reduction in diastolic pressure should be avoided in patients with CAD who are being treated for hypertension.

15. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial.[see comment]. *JAMA.* Nov 10 2004;292(18):2217-2225.

CONTEXT: The effect of antihypertensive drugs on cardiovascular events in patients with coronary artery disease (CAD) and normal blood pressure remains uncertain. OBJECTIVE: To compare the effects of amlodipine or enalapril vs placebo on cardiovascular events in patients with CAD. DESIGN, SETTING, AND PARTICIPANTS: Double-blind, randomized, multicenter, 24-month trial (enrollment April 1999-April 2002) comparing amlodipine or enalapril with placebo in 1991 patients with angiographically documented CAD (>20% stenosis by coronary angiography) and diastolic blood pressure <100 mm Hg. A substudy of 274 patients measured atherosclerosis progression by intravascular ultrasound (IVUS). INTERVENTIONS: Patients were randomized to receive amlodipine, 10 mg; enalapril, 20 mg; or placebo. IVUS was performed at baseline and study completion. MAIN OUTCOME MEASURES: The primary efficacy parameter was incidence of cardiovascular events for amlodipine vs placebo. Other outcomes included comparisons of amlodipine vs enalapril and enalapril vs placebo. Events included cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, and new diagnosis of peripheral vascular disease. The IVUS end point was change in percent atheroma volume. RESULTS: Baseline blood pressure averaged 129/78 mm Hg for all patients; it increased by 0.7/0.6 mm Hg in the placebo

group and decreased by 4.8/2.5 mm Hg and 4.9/2.4 mm Hg in the amlodipine and enalapril groups, respectively (P<.001 for both vs placebo). Cardiovascular events occurred in 151 (23.1%) placebo-treated patients, in 110 (16.6%) amlodipine-treated patients (hazard ratio [HR], 0.69; 95% CI, 0.54-0.88 [P = .003]), and in 136 (20.2%) enalapril-treated patients (HR, 0.85; 95% CI, 0.67-1.07 [P = .16]. Primary end point comparison for enalapril vs amlodipine was not significant (HR, 0.81; 95% CI, 0.63-1.04 [P = .10]). The IVUS substudy showed a trend toward less progression of atherosclerosis in the amlodipine group vs placebo (P = .12), with significantly less progression in the subgroup with systolic blood pressures greater than the mean (P = .02). Compared with baseline, IVUS showed progression in the placebo group (P<.001), a trend toward progression in the enalapril group (P = .08), and no progression in the amlodipine group (P = .31). For the amlodipine group, correlation between blood pressure reduction and progression was r = 0.19, P = .07. CONCLUSIONS: Administration of amlodipine to patients with CAD and normal blood pressure resulted in reduced adverse cardiovascular events. Directionally similar, but smaller and nonsignificant, treatment effects were observed with enalapril. For amlodipine, IVUS showed evidence of slowing of atherosclerosis progression.

16. Ried LD, Tueth MJ, Taylor MD, Sauer BC, Lopez LM, Pepine CJ. Depressive symptoms in coronary artery disease patients after hypertension treatment. *Annals of Pharmacotherapy.* Apr 2006;40(4):597-604.

BACKGROUND: Depression is highly prevalent and frequently recurs in patients with coronary artery disease (CAD) and hypertension. Certain medications used to treat hypertension are alleged to be associated with higher risk of depression. OBJECTIVE: To compare depressive symptoms before and during treatment with 2 equivalent hypertension treatment strategies in patients with CAD stratified according to a self-reported history of physician-diagnosed depression. METHODS: Patients enrolled in a randomized hypertension treatment study were mailed baseline and one year follow-up surveys and stratified according to a self-reported history of depression. Patients (N = 1152) were 50 years old or older with hypertension and clinically stable CAD. Depressive symptoms were measured using the Center for Epidemiologic Studies-Depression (CES-D). High risk of depression was defined as a history of physician-diagnosed depression reported by patients on the baseline survey. Depressive symptoms were compared for verapamil sustained-release (SR)- and atenolol-based hypertension treatment. RESULTS: Among patients with a previous history of depression, depressive symptoms improved over the one year follow-up period for patients assigned to both treatment regimens. Depressive symptoms improved for patients with no depression history in the verapamil SR group (p < 0.001) and were unchanged in the atenolol group (p = 0.52). Patients assigned to the atenolol-based strategy without prior history of depression were more likely to worsen 5 or more points on the CES-D. CONCLUSIONS: When antihypertensive treatment options are clinically equivalent, prescribers may first consider using a verapamil SR-based strategy, especially in patients with CAD who have no history of depression.

17. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes.[see comment]. *New England Journal of Medicine.* Nov 4 2004;351(19):1941-1951.

BACKGROUND: The multicenter double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) was designed to assess whether angiotensin-converting-enzyme inhibitors and non-dihydropyridine calcium-channel blockers, alone or in combination, prevent microalbuminuria in subjects with hypertension, type 2 diabetes mellitus, and normal urinary albumin excretion. METHODS: We studied 1204 subjects, who were randomly assigned to receive at least three years of treatment with trandolapril (at a dose of 2 mg per day) plus verapamil (sustained-release formulation, 180 mg per day), trandolapril alone (2 mg per day), verapamil alone (sustained-release formulation, 240 mg per day), or placebo. The target blood pressure was 120/80 mm Hg. The primary end point was the development of persistent microalbuminuria (overnight albumin excretion, > or =20 microg per minute at two consecutive visits). RESULTS: The primary outcome was reached in 5.7 percent of the subjects receiving trandolapril plus verapamil, 6.0 percent of the subjects receiving trandolapril, 11.9 percent of the subjects receiving verapamil, and 10.0 percent of control subjects receiving placebo. The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression) adjusted for predefined baseline characteristics was 0.39 for the comparison between verapamil plus trandolapril and placebo (P=0.01), 0.47 for the comparison between trandolapril and placebo (P=0.01), and 0.83 for the comparison between verapamil and placebo (P=0.54). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively. Serious adverse events were similar in all treatment groups. CONCLUSIONS: In subjects with type 2 diabetes and hypertension but with normoalbuminuria, the use of trandolapril plus verapamil and trandolapril alone decreased the incidence of microalbuminuria to a similar extent. The effect of verapamil alone was similar to that of placebo. Copyright 2004 Massachusetts Medical Society.

18. Vranic II, Matic M, Perunicic J, Simic T, Soskic L, Milic N. Adenosine cardioprotection study in clinical setting of paroxysmal supraventricular tachycardia. *Prostaglandins Leukotrienes & Essential Fatty Acids.* Jun 2006;74(6):365-371.

PSVT attack of >20min and frequency >160 is well-recognized model of myocardial dysfunction. We measured 6-keto-PGF1alpha and TXB(2) before and after adenosine administration to assess its cardioprotective potential. A total of 64 patients were randomly assigned as having acute episode of PSVT to adenosine or verapamil group. A bolus of 6mg of adenosine up to the maximum dose of 12 or 5mg of verapamil up to the maximum dose of 10mg were given, until the sinus rhythm was restored. The levels of PGI(2), TXA(2) and TAS were measured in three different time intervals. In adenosine group all parameters were normalized after 20min of conversion to sinus rhythm. The ratio of PGI(2)/TXA(2) increased after 5min of conversion to SR (P<0.01). Also, the ratio of TXA(2)/TAS was decreased for ADO (P<0.01). This is the first study to demonstrate that adenosine exerts cardioprotective effect.

19. Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Archives of Internal Medicine.* Jun 27 2005;165(12):1401-1409.

BACKGROUND: Optimal first-step antihypertensive drug therapy in type 2 diabetes mellitus (DM) or impaired fasting glucose levels (IFG) is uncertain. We wished to determine

whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor decreases clinical complications compared with treatment with a thiazide-type diuretic in DM, IFG, and normoglycemia (NG). METHODS: Active-controlled trial in 31 512 adults, 55 years or older, with hypertension and at least 1 other risk factor for coronary heart disease, stratified into DM (n = 13 101), IFG (n = 1399), and NG (n = 17 012) groups on the basis of national guidelines. Participants were randomly assigned to double-blind first-step treatment with chlorthalidone, 12.5 to 25 mg/d, amlodipine besylate, 2.5 to 10 mg/d, or lisinopril, 10 to 40 mg/d. We conducted an intention-to-treat analysis of fatal coronary heart disease or nonfatal myocardial infarction (primary outcome), total mortality, and other clinical complications. RESULTS: There was no significant difference in relative risk (RR) for the primary outcome in DM or NG participants assigned to amlodipine or lisinopril vs chlorthalidone or in IFG participants assigned to lisinopril vs chlorthalidone. A significantly higher RR (95% confidence interval) was noted for the primary outcome in IFG participants assigned to amlodipine vs chlorthalidone (1.73 [1.10-2.72]). Stroke was more common in NG participants assigned to lisinopril vs chlorthalidone (1.31 [1.10-1.57]). Heart failure was more common in DM and NG participants assigned to amlodipine (1.39 [1.22-1.59] and 1.30 [1.12-1.51], respectively) or lisinopril (1.15 [1.00-1.32] and 1.19 [1.02-1.39], respectively) vs chlorthalidone. CONCLUSION: Our results provide no evidence of superiority for treatment with calcium channel blockers or angiotensin-converting enzyme inhibitors compared with a thiazide-type diuretic during first-step antihypertensive therapy in DM, IFG, or NG.

Head to Head Trials

20. Kojima S, Shida M, Yokoyama H. Comparison between cilnidipine and amlodipine besilate with respect to proteinuria in hypertensive patients with renal diseases. *Hypertension Research - Clinical & Experimental.* Jun 2004;27(6):379-385.

Unlike other dihydropyridine calcium channel blockers (CCBs), cilnidipine has been reported to exert an N-type calcium-channel-blocking activity and to reduce sympathetic hyperactivity. This study compared cilnidipine and amlodipine with respect to their effects on renal function and proteinuria. Twenty-eight proteinuric hypertensive outpatients (13 men and 15 women, aged 62+/-2 years) who had been maintained on CCBs for more than 3 months were randomly assigned to a group receiving amlodipine besilate (14 patients) or a group receiving cilnidipine (14 patients). CCBs were increased in dosage or other drugs were added until blood pressure decreased below 140/90 mmHg, but no inhibitors of the renin-angiotensin (RA) system were added or changed in dosage. Before and at 6 and 12 months after randomization, the concentrations of urine protein, urine albumin, serum and urine creatinine (Cr), and serum beta2-microglobulin were determined. The amlodipine group showed a significant increase in proteinuria, while the increase was suppressed in the cilnidipine group. The rate of increase in proteinuria at 12 months was 87% (95% confidence interval (CI) -10 to 184) of the baseline value with amlodipine and 4% (95% CI -69 to 77) of baseline with cilnidipine, a significant intergroup difference ($p<0.05$). The mean blood pressure remained in the 96-99 mmHg range until 12 months after randomization, showing no significant difference between the two groups. The cilnidipine group showed an increase in serum Cr levels (baseline vs. 12 months, 1.36+/-0.20 vs. 1.50+/-0.23 mg/dl, $p<0.01$). Overall, an inverse correlation existed between the changes in Cr and proteinuria ($r= -0.477$, $p<0.01$). These results

suggest that cilnidipine results in a greater suppression of the increase in proteinuria and greater reduction in glomerular filtration rate than amlodipine, and that these effects are similar between cilnidipine and RA inhibitors. However, additional large-cohort and longer-term studies will be needed to clarify whether cilnidipine is superior to other CCBs in maintaining renal function.

21. Vora A, Karnad D, Goyal V, et al. Control of rate versus rhythm in rheumatic atrial fibrillation: a randomized study.[see comment]. *Indian Heart Journal.* Mar-Apr 2004;56(2):110-116.

BACKGROUND: Patients with rheumatic heart disease and atrial fibrillation incur significant morbidity and mortality. It is not known which approach, rate control or maintenance of sinus rhythm might be most appropriate. The present study was undertaken to compare the strategy of ventricular rate control versus maintenance of sinus rhythm in rheumatic atrial fibrillation, and to evaluate the role of amiodarone in this patient population. METHODS AND RESULTS: We prospectively studied 144 patients with chronic rheumatic atrial fibrillation in a double-blind protocol-rhythm control (group I: 48 patients each with amiodarone -group Ia; and placebo -group Ib) and compared the effects with the ventricular rate control (group II) by diltiazem (n=48, open-label). Direct current cardioversion was attempted in group I. The mean age of the study population was 38.6+/-10.3 years, left atrial size was 4.7+/-0.6 cm, atrial fibrillation duration was 6.1+/-5.4 years, and 72.9% patients had undergone valvular interventions. At 1 year, 45 patients with sinus rhythm in group I compared to 48 patients in group II demonstrated significant increase in exercise to sinus rhythm time, had improvement in functional class and quality of life score. There was no difference in hospitalization rates, systemic bleeds or incidence of thromboembolism. Five patients died in group II but none in group I (p=0.02). In group I, 73/87 (83.9%) patients converted, and 45/86 (52.3%) patients maintained sinus rhythm at 1 year. Conversion rates were 38/43 (88.4%) with amiodarone versus 34/44 (77.3%) with placebo (p=0.49): corresponding rate for maintaining sinus rhythm was 29/42 (69.1%) versus 16/44 (36.4%), p=0.008 respectively. CONCLUSIONS: Maintenance of sinus rhythm appeared to be superior to ventricular rate control in patients with rheumatic atrial fibrillation in terms of an effect on mortality and morbidity. Sinus rhythm could be restored in the majority and amiodarone was superior to placebo in this regard.

Non-RCT Study (Follow-up Study based on RCT)

22. Hjemdahl P, Eriksson SV, Held C, Forslund L, Nasman P, Rehnqvist N. Favourable long term prognosis in stable angina pectoris: an extended follow up of the angina prognosis study in Stockholm (APSIS). *Heart.* Feb 2006;92(2):177-182.

OBJECTIVE: To evaluate the long term prognosis of patients with stable angina pectoris. DESIGN: Registry based follow up (median 9.1 years) of patients participating in the APSIS (angina prognosis study in Stockholm), which was a double blind, single centre trial of antianginal drug treatment. PATIENTS: 809 patients (31% women) with stable angina pectoris < 70 (mean (SD) 59 (7) years at inclusion) and an age and sex matched reference population from the same catchment area. INTERVENTIONS: Double blind treatment with metoprolol or verapamil during 3.4 years (median), followed by referral for usual care with open treatment. MAIN OUTCOME MEASURES: Cardiovascular (CV) death and non-fatal myocardial infarction (MI) in the APSIS cohort and total

mortality in comparison with reference subjects. RESULTS: 123 patients died (41 MI, 36 other CV causes) and 72 had non-fatal MI. Mortality (19% v 6%, p < 0.001) and fatal MI (6.6% v 1.6%, p < 0.001) were increased among male compared with female patients. Diabetes, previous MI, hypertension, and male sex independently predicted CV mortality (p < 0.001). Diabetes greatly increased the risk in a small subgroup of female patients. Male patients had higher mortality than men in the reference population during the first three years (cumulative absolute difference 3.8%) but apparently not thereafter. Female patients had similar mortality to women in the reference population throughout the 9.1 years of observation. CONCLUSIONS: Female patients with stable angina had similar mortality to matched female reference subjects but male patients had an increased risk. Diabetes, previous MI, hypertension, and male sex were strong risk factors for CV death or MI.

Placebo-Controlled Trials

23. Liu L, Zhang Y, Liu G, et al. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients.[see comment]. *Journal of Hypertension.* Dec 2005;23(12):2157-2172.

OBJECTIVE: To compare the incidence of stroke and other cardiovascular events in hypertensive patients receiving a low-dose diuretic and low-dose calcium antagonist combination with those receiving low-dose diuretic monotherapy, and assess the effects of a small blood pressure difference at achieved levels lower than those achieved in previous placebo-controlled trials. METHODS: The Felodipine Event Reduction (FEVER) trial was an investigator-designed, prospective, multicentre, double-blind, randomized, placebo-controlled, parallel group trial. It enrolled 9800 Chinese patients, of either sex, aged 50-79 years, with one or two additional cardiovascular risk factors or disease, whose blood pressure, 6 weeks after switching from previous antihypertensive therapy to low-dose (12.5 mg a day) hydrochlorothiazide, was in the range 140-180 mmHg (systolic) or 90-100 mmHg (diastolic). These patients were randomly assigned either to low-dose felodipine extended release or placebo, and followed at 3-month intervals for an average of 40 months. RESULTS: The intention-to-treat analysis included 9711 randomly selected patients with only 30 (0.3%) lost to follow-up. A total of 31 842 patient-years of follow-up were accumulated, with 85.9% of patients remaining on blinded randomized treatment. Add-on therapy was given to 33.9% of the hydrochlorothiazide-felodipine patients and to 42.3% of the hydrochlorothiazide-placebo patients. In the felodipine group, systolic blood pressure (SBP)/diastolic blood pressure (DBP) decreased (from randomization to study end) from 154.2/91.0 to 137.3/82.5 mmHg, and in the placebo group from 154.4/91.3 to 142.5/85.0 mmHg, with an average difference throughout the trial of 4.2/2.1 mmHg. In the felodipine group, the primary endpoint (fatal and non-fatal stroke) was reduced by 27% (P = 0.001). Among secondary endpoints, all cardiovascular events were reduced by 27% (P < 0.001), all cardiac events by 35% (P = 0.012), death by any cause by 31% (P = 0.006), coronary events by 32% (P = 0.024), heart failure by 30% (P = 0.239), cardiovascular death by 33% (P = 0.019), cancer by 36% (P = 0.017) in the felodipine group. No significant differences were found in new-onset diabetes. Both treatments were very well tolerated. CONCLUSIONS: In moderately complicated hypertensive patients from China even a difference in SBP/DBP as small as 4/2 mmHg, such as that induced by adding low-dose felodipine to low-dose hydrochlorothiazide, is associated with very substantial reductions in the incidence of

most types of cardiovascular events. As the SBP achieved in the felodipine group was below the recommended goal of less than 140 mmHg, and SBP in the placebo group was slightly above that level, FEVER provides the required evidence in support of the guidelines recommended goal, even for a hypertensive population not entirely consisting of patients with diabetes or previous cardiovascular events.

24. Lubsen J, Wagener G, Kirwan B-A, de Brouwer S, Poole-Wilson PA, investigators A. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension: the ACTION trial.[see comment]. *Journal of Hypertension.* Mar 2005;23(3):641-648.

OBJECTIVE: To examine the effects of nifedipine GITS on clinical outcome in patients with concurrent stable angina and hypertension. METHODS: Data from the double-blind placebo-controlled ACTION trial was stratified for hypertension (blood pressure > or = 140/90 mmHg), at baseline. RESULTS: A total of 52% of 7665 ACTION patients were hypertensive. Some 80% were on a beta blocker; hypertensives were more often treated with other blood pressure-lowering drugs. Mean baseline blood pressure was 122/74 mmHg among normotensives and 151/85 mmHg among hypertensives. Follow-up blood pressures were reduced by nifedipine ($P < 0.001$) on the average by 3.9/2.4 and 6.6/3.5 mmHg among normotensives and hypertensives, respectively. Nifedipine GITS significantly ($P < 0.05$) reduced the combined incidence of all-cause mortality, myocardial infarction, refractory angina, heart failure, stroke and peripheral revascularization by 13% in hypertensives only. Nifedipine significantly reduced the incidence of any stroke or transient ischemic attack by almost 30% in both subgroups and the need for coronary angiography by 21% in normotensives and 16% in hypertensives. Among hypertensives, the incidence of new overt heart failure was significantly reduced by 38% and of debilitating stroke by 33%. Among normotensives, the need for coronary bypass grafting was significantly reduced by 32%. Nifedipine did not affect all-cause death, cardiovascular death and myocardial infarction in either normo- or hypertensives, but increased the need for peripheral revascularization. CONCLUSION: The salutary effects of the addition of nifedipine GITS to the basic regimen of patients with concurrent stable symptomatic coronary artery disease and hypertension emphasize the need for blood pressure control.

APPENDIX B